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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WALICKA, MALGORZATA A	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 07/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/622,893	YUAN ET AL.	
	Examiner	Art Unit	
	Malgorzata A. Walicka	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-86* is/are pending in the application.

4a) Of the above claim(s) *26-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24 and 32-86* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 July 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *04/30/04 & 04/05/05*
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RD

Response to Restriction Requirement filed April 16, 2005 is acknowledged. Claims 1-86 are pending. Claims 1-25 and 32-86 are under examination. Claims 26-31 are withdrawn form examiner's consideration as being drawn to the non-elected invention; see 37 CFR 1.142(b).

Detailed Action

1. Restriction/election

Applicant's election, with traverse, of Group I, claims 1-25, 32, 33-58 and 62-82, drawn to a chimeric protein comprising amadoriase, a kit comprising said protein and its method of use is acknowledged. The traversal is on the ground(s) that claims 59-61 and 83-86 are not included in Group I. Since Group II consists of claims 26-31 claims 59-61 and 83-86 were inadvertently not included in Group I. Claims of Group I, i.e., 1-25 and 32-86 are under examination.

2. Objections

Specification

The description of Fig. 1 on page 3 is objected to as containing the abbreviation GSP that is not expanded. The description of Fig. 2 is not in a proper idiomatic English. The description of Fig. 3 and 5 are objected to because it does not describe what in Fig. 3 reacts with fructosyl valine and what signal is referred to in Fig.5.

The catalog number for Fructosamine Calibrator on page 27 lacks a name of the producer.

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors in the specification of which applicant may become aware.

Figures

Fig. 3 lacks description of Y-axis.

Claims

Claim 32 is objected to as depending on nonelected claim 31.

3. Rejections

3.1. *35 USC § 112, second paragraph*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 54 and 78are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are confusing in limiting inactivation of protease by heat currently with the presence of the chimeric protein. Inactivation of protease by heat performed in the presence of chimeric protein is likely to inactivate the chimeric protein as well, making the method inoperative.

Claim 85 is confusing, because when amadoriase and peroxidase are in the same solution, peroxidase will oxidize amadoriase preventing it from deglycating peptides and amino acids.

3.2. 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3.2.1. Written description

Claims 1-10, 12, 14-24, 32-42, 45-66, 69-86 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims are rejected because the structure or structure and function of the claimed product which is to be used in the claimed methods and kits lack sufficient written description. The claims are very broad as to the structure of the amadoriase and signal molecules used for

construction of a chimeric protein. The disclosure does not teach how to modify SEQ ID NO:3 so that a sequence having 40% homology was still having amadoriase activity. Furthermore, it is unknown what the function of SEQ ID NO: 1 and 4 has to be so that the sequences having at least 40% of homology and retaining the function could be used for construction of the claimed chimeric proteins. Applicants disclosed only two species of the broadly claimed genus of products, and methods of their use as well as kits for performing said methods. The species are amadoriase of SEQ ID NO: 3 having SEQID NO: 1 attached to its N-terminus, and protein of SEQ ID NO: 5 consisting of SEQ ID NO: 1, SEQ ID NO: 3 and SEQ ID NO: 4. Neither of these species is sufficient to identify a broad genus of chimeric proteins claimed by the Applicants. Thus, because the structure and function of the claimed genus of products is not sufficiently disclosed i.e., because the claims are lacking sufficient written description of structure and function, one skilled in the art is not convinced that Applicants were in possession of the claimed invention at the time the application was filed.

The Applicants' attention is turned to the fact that structural limitations recited by claim 12 are so minor that the scope of the claimed proteins covers many proteins with virtually no structural homology to SEQ ID NO:3 at all. The reason is that since an epitope may contain only 5 amino acids there are many epitopes in SEQ ID NO: 3, thus an antibody that binds SEQ ID NO: 3 binds many other unrelated proteins.

3.2.2. Scope of enablement

Claims 1-12, 14-24, 32-42, 45-66, 69-86 are also rejected for scope of enablement, because the specification, while being enabling for the chimeric protein consisting of SEQ ID NO: 1 attached to N-terminus of SEQ ID NO: 3, or for chimeric protein identified by SEQ IID NO: 5 as well as the methods of their use and kits for said methods, does not reasonably provide enablement for any chimeric protein comprising:

1) any amadoriase, including a protein having at least 40 % identity to SEQ ID NO:3,

2) any peptidyl leader that is 40% identical to SEQ ID NO: 1 or 4 and any amadoriase,

3) any bacterial leader, any amadoriase and any second bacterial leader,

as well as methods of use of said chimeric protein use and kits for the methods.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Otherwise, undue experimentation is necessary to make the claimed invention.

Factors to be considered in determining whether undue experimentation is required are summarized *In re* Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill

of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

The nature and breath of the claimed invention encompasses a product that is a chimeric protein comprising one or two peptidyl leaders and an amadoriase. Furthermore, the invention relates to a methods of use of said chimeric protein and a kit comprising said chimeric protein. The amadoriase is any amadoriase, originating from any natural or man-made source or an amadoriase that has at least 40% identity to SEQ ID NO:3. The peptidyl leader is any peptidyl leader form any natural or human made-made source or any leader that is at least 40% identical to SEQ ID NO: 1 or 4.

While methods of construction chimeric proteins are well known in the relevant art, and skills of the artisans highly developed, to make any chimeric protein outlined 1)-3) above is out of routine experimentation. The specification does not teach that any combination of peptidyl leaders and any amadoriase retains amadoriase function; see the above rejection for lack of written description. Thus one of skill in the art is forced to test many combinations before he/she will find the proper one. Furthermore, the function of SEQ ID NO: 1 or 4 is not disclosed and the specification is silent about in the how to modify the structure of SEQ ID NO: 1 and 4 so that the encoded peptidyl leaders and the chimeric protein for which they are used retained the desired function. Although Applicants include conservative amino acid substitution in the description of the invention, this is not enabling for constructing a chimeric protein comprising polypeptidyl leaders being at least 40% identical to SEQ ID NO: 1 or 4 and any amadoriase. There is no guidance how to modify SEQ ID NO:3 so as the sequence

having 40% identity retained amadoriase acitivty. The lack of guidance on the part of Applicants how to modify SEQ ID NO: 1, 3 and 4 and which peptidyl leaders in combination with which amadoriase give functional chimeric proteins 2) and 3) mentioned above imposes on one skilled in the art an extensive experimentation wherein the probability of success in obtaining the claimed invention is low.

Examiner concludes that without a further detailed guidance on the part of Applicants regarding the structure and function of the claimed chimeric proteins experimentation left to those skilled in the art is improperly extensive and undue.

In addition, Applicants attention is turned to the fact that claims 45 and 69 are not enabled because there are no known methods for measuring changes in amount of H_2O in an aqueous assays as changes in amount of water cased by deglycation is negligible compared to the amount of water present in the reaction vessel.

3.3. 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.

Patentability shall not be negatived by the manner in which the invention was made.

3.3.1. Claims 1-2, 6-14, 21-22 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yoshida et al. (Primary structures of fungal fructosyl amino acid oxidases and their application to the measurement of glycated proteins, Eur. Biochem. 1996, 242, 499-5050, Takahashi et al. **A** (Molecular Cloning and Expression of Amadoriase Isoenzyme (Fructosyl Amine-oxygen Oxidoreductase EC 1.5.3) from Aspergillus *fumigatus,* J. Biol. Chemistry 1997, 6, 12505-12307) in view of common knowledge in the field of protein expression as exemplified by US Patent 6,194,200 (Expression Systems for Preparation of Polypeptides in Procaryotic cells, issued Feb. 27, 2001) further referred to as US Patent. The all documents are included in IDS.

Yoshida et al teaches the use of several amadioriases, among them of *Aspergillus* species, for determination of the level of blood protein glycation in diabetic patients.

Takahashi et al. teach amadoriase from *Aspergillus sp.* that consists of 438 amino acid residues of which amino acids 2-438 are identical to amino acids 1-437 of SEQ ID NO: 3 of the instant application. Takahashi at al emphasize it is the protein consisting of amino acids residues 2-438 which is routinely purified form *Aspergillus* and; see the comment on page 12306, right column, line 4-6 and N-terminal sequence of amadoriase II in Table IV, page 3443 of the reference Takahashi **B** bellow mentioned in the comment.

Takashi et al. do not disclose a chimeric protein, which comprises a bacterial leader sequence and an amadoriase, however, it is a routine practice in the field of protein expression to express proteins as chimeras containing bacterial leader sequences because these sequences promote secretion and stabilize the expressed protein; see US Patent, Introduction.

It would have been obvious to one having ordinary skill in the art at the time of invention to have a protein consisting of amino acid residues 2-438 of Takahashi et al. amadoriase II and add to its N-terminus a bacterial leader as taught by the US Patent.

The motivation for the modification would be an improvement of the enzyme productivity so as to have a large quantity of pure stable enzyme necessary for measurements of glycated proteins in blood serum. This motivation is provided by Yoshida et al. on page 505, the last sentence. The expectation of success is high because of well-developed and routine use of expressed fusion protein in the art. The leader sequences usually do not interfere with the biological activity of the protein of interest, thus the protein of interest may be used as a fusion protein; see the abstract of the US Patent.

Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made, and was as a whole *prima facie* obvious.

3.3.2. Claims 33-37, 39-41, 45, 53, 54, 57, 58, 59-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over European Patent EP0 821064 A2, published Jan. 28,

1998 (the EU Patent), included in the IDS, and further in view of Takahashi et al. A and US Patent 6,194,200 as used in the above rejection of the chimeric protein of claim 1.

Claims 33-37, 39-41, 45, 53, 54, 57, 58 are directed to the use of the protein of claim 1 in a method for assaying a glycated protein in a sample. Claims 59-61 are directed to the kit for such method.

The EU Patent discloses in Examples 6 and 7, page 16, a method of measurement of the level of glycation of a protein, namely of serum albumin and hemoglobin, which consists of the same steps as those of claim 33. The method uses fructosyl amino acid oxidase (amadoriase) from *Aspergillus terreus.*

It would have been obvious to one having ordinary skills in the art to modify teachings of the EU Patent and replace fructosyl amino acid oxidase (amidoriase) from *Aspergillus terreus* with the chimeric protein of the invention.

The motivation for the modification would be to have a method of measurements of glycated protein in human blood for clinical uses. The motivation is provided by the EU Patent on page 2, line 21-25, wherein one can read: "As the concentration of these derivatives [glycated proteins] in blood reflects an average of blood sugar levels over a particular period of time it can be used as a significant index for diagnosis and control of conditions of diabetes." The expectation of success is high because of routine use in the art of amadoriases of different origin in said method. Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made, and was as a whole *prima facie* obvious.

The additional features of the method recited by claims 38, 40, 42, 46-52, 55-56 are well known features of such amadoriase based assays for the art.

3.3.3. Claims 62-63, 65, 66, 83 and 85 are rejected as being unpatentable over European Patent EP0 821064 A2, published Jan. 28, 1998 (included in the IDS), in view of common knowledge in biochemistry and Takahashi et al. **B** (Isolation, Purification and Characterization of Amadoriase Isoenzymes (Fructosyl Amine-oxygen Oxidoreductase EC1.5.3) form *Aspergillus* sp., J. Biol. Chem., 1007, 272, 3437-3443).

Claims 62-63 and 65 are directed to a method for assaying a glycated protein in a sample using protein K and amadoriase. Claim 66-68 are directed to a method for assaying a glycated protein in a sample using protein K and amadoriase which is a protein of invention. Claims 83 is directed to the kit for the method of claim 62, claims 85 to the kit of method of claim 66.

The EU Patent discloses a method for assaying a glycated protein in a sample using proteinase XIV and an amadoriase from *Aspergillus terreus*. The patent does not disclose a method using proteinase K as a proteinase, however, those of skill in the art realize that proteinse K is degrading proteins similarily as proteinase XIV does.

It would have been obvious to one having ordinary skill in the art to modify teachings of the EU Patent and replace proteinase XIV with proteinase K, which degrades glycated proteins as well as protease does; absent teaching to the contrary.

It would have been further obvious to one having ordinary skill in the art to modify teachings of the EU Patent and replace fructosyl amino acid oxidase (amidoriase) from *Aspergillus terreus* with any other amidoriase that does the job. Particularly one of ordinary skills in the art would use a chimeric protein of invention because Takahashi et al. teach that the amadoriase II of *Aspergillus* sp. which is used in the fusion protein of the invention can deglycate many glycated amino acids very efficiently; see Takahashi B, Table II, page 3442 and *Assays for enzymatic activity* on page 3438.

The motivation would be to have a method of measurements of glycated protein in human blood for clinical uses. The motivation is provided by the EU Patent on page 2, line 21-25, wherein one can read: "As the concentration of these derivatives in blood reflects an average of blood sugar levels over a particular period of time it can be used as a significant index for diagnosis and control of conditions of diabetes." The expectation of success is high because of routine use in said method of various proteases and amadoriases. Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made, and was as a whole *prima facie* obvious.

The additional features of the method recited by claims 64, 69-82 and 84-85 are well known features of such amadoriase based assays for the art.

4. Conclusion

All claims are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka whose telephone number is (571) 272-0944. The examiner can normally be reached on Monday-Friday from 10:00 a.m. to 4:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Patent Examiner

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